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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/391,861	09/07/1999	ARLEN READ THOMASON	99.371	9209

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/391,861	Applicant(s) Thomason
	Examiner Dave Nguyen	Art Unit 1632

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 16, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5, 7-13, and 39-43* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 7-13, and 39-43* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 18
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 36-38, 44-46 have been canceled, claims 1, 2, 8, 13, 39, 40, 42 have been amended, claim 47 has been added by the amendment filed September 25, 2002.

Applicant's election without traverse of the group II claims in the response filed January 27, 2003 is acknowledged.

Claims 2, 8 have been amended, claim 47 has been canceled by the amendment filed January 16, 2003.

Claims 1-5, 7-13, 39-43 are pending for examination.

It is noted that during the telephone interview with applicants 'representative Devin Noonan on April 5, 2002, the examiner indicated that with respect to murine FGF-like molecules of SEQ ID NOS 2 and 4, the 101 rejection of record will be withdrawn by the examiner. However, after a further consideration and consultation with the examiner's supervisor, Debbie Reynolds, the examiner's indication during the telephone interview is not correct and the 101 rejection for all of presently pending claims is maintained for the reasons of record, *e.g.,* see pages 2 and 3 of the office action dated January 4, 2001, and for the following reasons:

It is clear from the instant specification that the " FGF-like polypeptide " protein described as SEQ ID NO: 3 or SEQ ID NO: 4 are claimed as being similar to other known FGF members of the FGF family, wherein the members are not necessarily related in its sustantial utility and essential structure for its corresponding biological function. There is little doubt that, after complete characterization, this DNA and protein, may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete, and thus, lacks a substantial utility for the claimed invention at the time the invention was made. The instant situation is directly analogous to that which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were know to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent

in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts where this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101 which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. Note that a utility that requires or constitutes carrying out further research or identify or reasonably confirm a real world context of use is not a substantial utility.

More specifically as to the reliance by applicant of the as-filed specification for an enormous number of utilities as indicated in the laundry list wherein many of the contemplated utilities are not even related or are even contradictory with one another, the as-filed specification discloses that a BLAST search indicates that SEQ ID NO: 4 in a BLAST search was found to be homologous or similar to other members of the FGF family of protein. The as-filed specification does not provide any information or written support to show a substantial utility for the subject matter being sought in the presently pending claims, particularly since it is well-recognized in the art that FGFs are members of a protein family which has demonstrated a broad range of biological activities involving cell growth and differentiation such as angiogenesis, morphogenesis, and wound healing. Galzie et al. (Biochem. Cell Biol. 75: 669-685, 1997), the FGF family is complex and diverse (see abstract). Table 1 of Galzie et al. details the biological significance of the first 9 members of this protein family, wherein none of the associated functions are found in common with any other family member.

Furthermore, the prior art of record demonstrates that the biological function of the protein family to which the disclosed protein is said to be a member is so diverse, that one could not predict which biological activity is possessed by the disclosed protein based on structural similarity alone, especially since all the members share structural similarity, but not functional similarity. Neither the as-filed specification nor the prior art of record at the time the invention was made provides any factual evidence to indicate that as the as-filed specification provides a substantial utility for the subject matter being sought in the presently pending claims.

Notwithstanding the laundry list of utilities as indicated in the as-filed application, the specification contemplates that the FGF-like molecules is secreted into the bloodstream where it may exert effects on

distal sites, and that the claimed FGF-like molecules (SEQ ID NOS 3 and 4) then may have a specific utility for stimulating cells within or near the liver, regulating intestinal cell activity, or stimulating pancreatic beta islet cells, the comments are not found persuasive because the fact that the as-filed specification contemplates that the claimed FGF-like molecules regulates growth and differentiation of cells within the liver and of other cell types after secretion from the liver, does not provide any credible support for a well-established, or a specific and substantially credible utility for the subject matter being sought in the presently pending claims. What is exactly the specific biological function of SEQ ID NO: 4 in growth, differentiation of cells in liver or of any other cell types on the basis of applicant's disclosure. In light of the fact that the FGF family of FGF proteins is enormous and involves a number of specific biological functions but distinct in growth and differentiation, one skilled in the art would not have recognized that the as-filed specification has provided any specific and substantial utility for the subject matter being sought in the presently pending claims. The specification as a whole clearly generalizes and merely speculates a number of potential utilities, some of which are not even related and are distinct and contrary to one another, *e.g.,* stimulating pancreatic beta islet cells, stimulating cells within or near the liver, regulating intestinal cell activity as opposed to the making of transgenic mice expressing any claimed FGF-like transgene that exhibit an abnormal phenotype generally characterized as inhibited or delayed maturation, which includes reduced body weight, reduced liver weight as percent of body weight (page 4 of the specification), stimulation of angiogenesis, and yet also inhibition of angiogenesis, therapeutics in treatment of diabetes and yet also therapeutics in treatment of corneal epithelium, lens, or retinal tissues, and yet also treatment of neuronal and/or hematopoietic cells (page 5 of the specification). These possible utilities-other than as a possible object of scientific inquiry-was not yet established by the as-filed specification at the time the invention was made.

A simple statement in the as-filed specification as to the similarity between the structure applicant's claimed FGF-like polypeptide and well-established FGF of the prior art, *e.g.,* 32% identify to FGF-6 and 28% identity to FGF-4 for SEQ ID ID NO: 3, which is the only main basis or nexus for applicant's claim of merely speculative or potential utility, which does not have a real world value and does not provide a

currently available specific benefit t the relevant public, and thus as a whole, does not meet the requirements of 35 USC 101.

Furthermore, all of the asserted utilities as indicated in the as-filed specification (pages 4 and 5) amounts to only generalized and non-specific utilities, wherein each of the asserted utilities requires additional knowledge about the **specifically biological function of any FGF-like transgene as encompassed by the claimed genus of nucleic acid sequences**, whether there are specific ligands and/or well-established biological pathway responsible for any of applicant's asserted utilities linked to applicant's claimed FGF like transgene, *e.g.,* if so, **their identity**. As a result, since each of applicant's asserted utilities requires additional knowledge about any of applicant's claimed FGF-like transgene before any of applicant's claimed FGF like-transgene can be used for a specific purpose or before a real word benefit exists in currently available form, the utility requirement has not been met, *e.g.,* where applicant's asserted utilities constitute research on the claimed product itself, there is not apparent *immediate* benefit to the public that the patent system is designed to protect.

In view of the reasons set forth in the stated rejection and in view of the reasons set forth in the preceding paragraphs, a skilled artisan would not have recognized that, **at the time the invention was made,** this as-filed specification provides any credible support for a substantial utility for the subject matter being sought in the presently pending claims.

Claim 1(c), (d), readable on genes and/or sequences which are not necessarily SEQ ID NO: 4, and yet must exhibit any of the activities as listed in the laundry list cited in the specification; claims 39-40 readable of nucleic acid sequences, which encode sequences other than SEQ ID NO: 4 but share at least a 25 amino acid fragment of SEQ ID NO: 4, and claim 2-5, 7-13, claims 5, 7-13, 41-43, which are dependent from the rejected claims are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention, for the reasons set forth in pages 4 and 5 of the office action dated January 4, 2001, and for the following reasons:

The as-filed specification does not meet the written description requirement for claiming a genus of nucleotide sequences which hybridizes under at least moderately stringent conditions to SEQ ID NO: 3 and DNA coding for SEQ ID NO: 4, and which exhibits any of the activities as listed in the laundry list cited in the specification, wherein the activities are in conflict of one another. An adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays and/or formula containing unspecified molecular structures of FGF like polypeptide encoded nucleotide sequences that are essential for the making the genuses of unspecified material(s) as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures, *e.g.,* primary sequence structure, of a representative number of sequences which are embraced by the claimed genus. In this instance, the as-filed specification only discloses SEQ ID NO: 4 with one of its contemplated activities being proven by the post-filing art.

It is not sufficient to support the present claimed invention directed to numerous number of nucleotide sequence(s) as claimed in claim 1(c), for example, with no specific chemical structure so as to exhibit one of applicant's intended utilities, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other material(s) of nucleotide sequence(s) of FGF-like transgene having any of the biological functions as contemplated by the specification and the claims, wherein the potential biological activity and its corresponding primary sequence, are not necessarily the same as that of the proven SEQ ID NO: 4, and are yet to be discovered. In light of the fact that the FGF family of FGF proteins is enormous and involves a number of specific biological functions but distinct in growth and differentiation, one skilled in the art would not have recognized that the as-filed specification has provided sufficient description of the claimed genus solely on basis of the human and murine SEQ ID NOS 2 and 4, respectively. The specification as a whole clearly generalizes and merely speculates a number of potential activites, some of which are not even related and are distinct and contrary to one another, *e.g.,*

stimulating pancreatic beta islet cells, stimulating cells within or near the liver, regulating intestinal cell activity as opposed to the making of transgenic mice expressing any claimed FGF-like transgene that exhibit an abnormal phenotype generally characterized as inhibited or delayed maturation, which includes reduced body weight, reduced liver weight as percent of body weight (page 4 of the specification and also asserted as a specific and substantially credible utility on page 8 of the response), stimulation of angiogenesis, and yet also inhibition of angiogenesis, therapeutics in treatment of diabetes and yet also therapeutics in stiulation of corneal epithelium, lens, or retinal tissues, and yet also treatment of neuronal and/or hematopoietic cells (page 5 of the specification). These possible activites-other than as a possible object of scientific inquiry-was not yet established by the as-filed specification at the time the invention was made. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of gene(s) that must possess any of the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed FGF-like transgenes that must exhibit any of the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's response (filed) has been considered by the examiner but is not found persuasive for the following reasons:

Claim 1(c), (d), 39 and 40 are still readable on genes and/or sequences which are not necessarily SEQ ID NO: 4, and yet must exhibit any of the activities as listed in the laundry list cited in the specification, and thus, the written description rejection is maintained for the reasons of record.

Applicant's latest response (pages 6 and 7) has been considered by the examiner but is not found persuasive for the reasons of record.

Claim 1(c), (d), 2-5, 7-13, 39-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly in view of the reasons of record and the following reasons.

In addition to the rejections set forth above, the as-filed specification does not provide sufficient guidance and/or evidentiary support to reasonably enable the broad scope of the claims 1(c), (d), 2, 5, 8, 9, 13, 42, and claims dependent there from. The state of the prior art indicates that FGF family members display a broad range of biological activities as mitogens, mitogens, angiogenic factors, neurotrophiic factors, differentiation factors, and oncogenes. Brenner (1999,Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12;425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that

one skilled in the art can not rely upon structural similarity alone to determine functionality of a reasonable number of sequences as claimed in claim 1(c) and (d), including sequences other than SEQ ID NOS 3 or 4 that meet the written description requirement, the specification fails to teach the skilled artisan how to prepare and use the claimed polynucleotides other than those as claimed in claims 39, 40, 1(a), 1(b), which preparation is relied upon solely on recombinant assays and BLASAT sequence comparison , without resorting to undue experimentation, particularly given the reasons set forth above. Notwithstanding an enormous number of proteins, allelic variants, orthologs, mutants thereof as broadly claimed in claim 1(a) an d(b), there is not even a specific disclosure or evidentiary support for a particular disease and/or biological activity correlatable to SEQ ID NO: 4 such that the claimed polypeptide can be used in a diagnostic assay. However, the relied evidence and/or activity is not supported by the as-filed application, and thus, claim 12 is not reasonably enabled on the basis of applicant's disclosure and the state of the prior art, particularly it would require an undue experimentation for a skilled artisan to determine which of the activities from the laundry list as cited in the as-filed specification would be putative for SEQ ID NO: 4. Further, the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. For example, while it is known that many amino acid substitutions
are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Ngo et al., 1994,The protein Folding problem and –tertiary Structure prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine, without undue experimentation, the positions in the protein and DNA which are tolerant to change and the nature and extent of changes that

can be made in these positions. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Brenner, 1999, Trends in Genetics 15: I32-I33; Bork et al., 1996, Trends in Gen.etics 12:425-427).

With respect to claims (claims 5 and 42) embracing a method of producing any FGF-like polypeptide recombinantly, which is not necessarily DNA encoding SEQ ID NO: 4, it is not apparent as to how a skilled artisan employed a host cell comprising the DNA to express such any FGF-like polypeptide, particularly given the reasons as set forth above.

With respect to claims 2, 9-11 embracing any host cell comprising any of DNAs encoding a FGF-like polypeptide, the specification only provides sufficient guidance for the making and preparation of a cultured or isolated host cell comprising the DNA as recited in claims 1(a), 1(b), 39 and 40. The claims as written are not necessarily limited to cultured or isolated host cells, and as such, it is not apparent how a skilled artisan to determine and/or prepare non-isolated or cultured cells as broadly claimed, particularly given the lack of any guidance for the making and preparation of such cells, and given that the state of the prior art for the making and use of transgenic animal comprising such cells remains reasonably predictable at the time the invention was made.

Due to the large quantity of experimentation unnecessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use any of the claimed protein, orthologs, variants, or fragment thereof to generate the infinite number of variants as recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity and the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In response to applicant' s assertion (the response, pages 7 and 8) that one skilled in the art would

know how to make and use and practice any of the subject matter now being sought in the claims, the comments are not found persuasive for the reasons set forth in the stated rejection, particularly since applicant's comments are conclusory, and express an opinion without any factual evidence to overcome the art-recognized limitations and reasons as set forth in the stated rejection.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1633

DAVE T. NGUYEN
PRIMARY EXAMINER